Exercise-induced right ventricular dysfunction is associated with ventricular arrhythmias in endurance athletes.

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Abstract

Introduction: Intense exercise places disproportionate strain on the right ventricle (RV) which may promote pro-arrhythmic remodelling in some athletes. RV exercise imaging may enable early identification of athletes at risk of arrhythmias.

Methods and results: Exercise imaging was performed in 17 athletes with RV ventricular arrhythmias (EA-VAs) of which 8 (47%) had an implantable cardiac defibrillator (ICD), 10 healthy endurance athletes (EAs) and 7 non-athletes (NAs). Echocardiographic measures included the RV end-systolic pressure-area ratio (ESPAR), RV fractional area change (RVFAC) and systolic tricuspid annular velocity (RV S'). Cardiac magnetic resonance (CMR) measures combined with invasive measurements of pulmonary and systemic artery pressures provided left ventricular (LV) and RV end-systolic pressure-volume ratios (SP/ESV), biventricular volumes and ejection fraction (EF) at rest and during intense exercise.

Resting measures of cardiac function were similar in all groups, as was LV function during exercise. In contrast, exercise-induced increases in RVFAC, RV S' and RVESPAR were attenuated in EA-VAs during exercise as compared with EAs and NAs ($P<0.0001$ for interaction group*workload). During exercise-CMR, decreases in RVESV and augmentation of both RVEF and RV SP/ESV were significantly less in EA-VAs relative to EAs and NAs ($p<0.01$ for the respective interactions). Receiver-operator characteristic curves demonstrated that RV exercise measures could accurately differentiate EA-VAs from subjects without arrhythmias [AUC for ΔRVESPAR =0.96 (0.89-1.00), $P<0.0001$].

Conclusion: Amongst athletes with normal cardiac function at rest, exercise testing reveals RV contractile dysfunction amongst athletes with RV arrhythmias. RV stress testing shows promise as a non-invasive means of risk-stratifying athletes.

Keywords:

Athletes – Right ventricle – Arrhythmias – Sports cardiology – Cardiac Magnetic Resonance imaging – Exercise – Arrhythmogenic Right Ventricular Cardiomyopathy - Echocardiography

Introduction

Amongst endurance athletes, ventricular arrhythmias most frequently arise from the RV. Whilst these ventricular arrhythmias of RV origin are most often benign[1], a significant incidence of major arrhythmic and fatal events have been described in some cohorts of athletes in association with structural, functional and electrical RV abnormalities[2-4]. The accurate identification of those few athletes with a potential for life threatening arrhythmias remains a major clinical challenge.

We have developed evidence supporting a hypothesis that the RV may be an "Achilles' heel" of the endurance athlete's heart. Whilst the LV remains relatively unaffected, the RV has to withstand a disproportionate hemodynamic load during intense exercise[5] resulting in transient exercise-induced RV dysfunction and chronic RV remodelling[5-11]. In a pre-clinical model, this exercise induced RV remodelling has been associated with a propensity to RV arrhythmias[12].

Using novel exercise echocardiography and real-time cardiac magnetic resonance (CMR) measures to assess RV function during exercise, we hypothesized that exercise could promote RV dysfunction in endurance athletes with ventricular arrhythmias (EA-VAs). We compared EA-VAs with healthy endurance athletes (EAs) and non-athletic controls (NAs) with the aim of a) validating the pathophysiological concept of exercise-induced pro-arrhythmic remodelling in humans, and b) developing a non-invasive clinical tool for differentiating healthy athletes from those with a propensity to serious arrhythmias.

Methods

Subjects

Endurance athletes with ventricular arrhythmias (EA-VAs) were recruited from an existing cohort at our institution in addition to new cases presenting over 36 months. The following inclusion criteria had to be fulfilled: a) current or previous participation in competitive sport and an intensive exercise training regime (at least 3x2 h per week); b) RV arrhythmias excluding idiopathic RVOT-VT, required to have a monomorphic left bundle branch block morphology i) sustained, or ii) non-sustained for ≥3 beats at a rate of ≥120 beats per minute, or iii) frequent isolated premature ventricular beats ≥2000/day. Athletes were included if the heart appeared morphologically normal or had appearances consistent with "athlete's heart", which was considered to include mild structural or functional abnormalities of the RV given that such changes have previously been described in healthy endurance athletes[5, 7, 11]. Many of the athletes could be described by the syndrome "exercise-induced"[2, 3] or "gene-elusive"[4] arrhythmogenic right ventricular cardiomyopathy (ARVC) whereby there is: a) mild structural and functional abnormalities sufficient to meet Task Force Criteria for a clinical diagnosis of ARVC[13], b) a protracted history of intense endurance exercise training and c) no evidence of inherited disease. Thus, all athletes underwent comprehensive evaluation and were excluded from participation if a mutation or variant of uncertain significance was identified in any of the five desmosomal genes associated with ARVC, or if there was clinical evidence of disease inheritance[3]. Athletes with moderate or severe RV abnormalities were excluded as this is not typical of an exercise-induced syndrome. Between 2011 and 2014, 25 athletes fulfilled the study inclusion criteria and 17 accepted to participate. Of these, 8 athletes had an implantable defibrillator (ICD). 15 of 17 EA-VAs were treated with beta-blockers or non-dihydropyridine calcium channel blockers alone or in combination with anti-arrhythmic medications. These medications were

withheld for at least 24 hours prior to exercise testing. All eligible volunteers were male and therefore only male subjects were recruited as control subjects.

The first 10 endurance athletes (EAs) responding to advertisements at local triathlon and cycling clubs who were competing in endurance sports and performing regular cycling and/or running training of >6 hours/ week were enrolled. 7 non-athletes (NAs) who were participating in recreational activity only (mild to moderate non-competitive exercise for <3 hours/week) were included. No subjects met exclusion criteria of known cardiovascular disease or abnormalities on ECG or echocardiogram.

The study protocol conformed to the Declaration of Helsinki and was approved by the local ethics committee. All subjects provided informed consent.

Study design

Cardiopulmonary exercise testing was performed on an upright cycle ergometer (ER900 and Oxycon Alpha, Jaeger, Germany). Breath-by-breath analysis provided measures of oxygen consumption at peak exercise (VO_2peak), ventilatory equivalent for carbon dioxide (VE/VCO_2 ratio) and maximal power output in Watts (Pmax). In those subjects with an ICD, the device was re-programmed such that all pacing and shocks were suspended during the exercise testing and none of the athletes with an ICD were paced. Having previously demonstrated that 66% of Pmax corresponded to the maximal sustainable exercise intensity in a supine position[14], we prescribed subsequent exercise efforts as: 25% ("low intensity"), 50% ("moderate intensity) and 66% ("peak intensity") of Pmax.

After at least 3 hours rest, echocardiography was performed at rest and during low-, moderate- and peak-intensity exercise using a programmable semi-supine ergometer with left lateral tilt (Easystress, Ecogito Medical sprl, Liege, Belgium).

The following day, all subjects (except the 8 EA-VAs with an ICD) underwent exercise CMR with simultaneous invasive pressure measurements. Prior to exercise, a 6 Fr pulmonary artery catheter was inserted under fluoroscopic guidance and a 20 gauge arterial catheter was placed in the radial artery. Pressure tracings were continuously acquired via a CMR compatible hemodynamic monitor (Maglife Serenity, Schiller AG, Baar, Switzerland).

Echocardiography

Resting and real-time exercise images were acquired using a Vivid E9 ultrasound system (GE Vingmed Ultrasound AS, Horten, Norway) and analysed offline using EchoPAC (version 112; GE Vingmed Ultrasound AS). Resting measures, including atrial and ventricular dimensions, early diastolic myocardial velocities and LVEF were acquired and analysed according to contemporary guidelines[15, 16]. RV outflow tract dimension (RVOTd) was measured in a parasternal short-axis view from the RV free wall to the aortic valve annulus and the RV inflow dimension (RVITd) was measured at the level of the tricuspid valve from an apical acquisition[16]. Two-dimensional global peak-systolic strain and strain rate (SRs) were quantified for the LV and RV on apical grey-scale images (60 – 90 frames/s) as described previously[17].

During exercise the following measures were obtained: a) LVEF and RVFAC from a single-plane four chamber view as described previously[17], b) RV free wall peak-systolic velocity (S') by tissue Doppler imaging (frame rate, 120–160 frames/sec), and c) Systolic pulmonary artery pressure (PASP) from the maximal trans-tricuspid regurgitant velocities without addition of right atrial pressure estimates. Enhancement of the Doppler signal with agitated colloid enhancement was used in all subjects as described previously[17]. As a surrogate of RV contractility, the RV end-systolic pressure area relationship (RV ESPAR) was calculated as PASP divided by RV end-systolic area[17].

CMR equipment, image acquisition and analysis

Biventricular volumes were measured during supine cycling exercise using a real-time CMR method which we have previously validated against invasive standards[14]. In brief, subjects performed supine exercise within the CMR bore using a cycle ergometer with adjustable electronic resistance (Lode, Groningen, The Netherlands). Images were acquired with a Philips Achieva 1.5T CMR with a five-element phased-array coil (Philips Medical Systems, Best, The Netherlands). Steady-state free precession cine imaging was performed without cardiac gating. A stack of 13 – 18 contiguous 8 mm image slices was acquired in the short-axis plane and subsequently in the horizontal long-axis plane.

Simultaneous with the image acquisition, ECG and respiratory timing were retrospectively synchronized using an in-house developed software program (RightVol, Leuven, Belgium) such that contouring could be performed at the same point of the respiratory cycle for all slices.

Biventricular volumes were calculated from endocardial contours traced on the short-axis (SAX) image with simultaneous reference to the horizontal long-axis (HLA) plane thus enabling the analysers (GC and ALG) to confirm the position of the atrio-ventricular plane. Total pulmonary resistance (tPVR) was calculated as the ratio of mean pulmonary artery pressure (mPAP) to CO and total systemic vascular resistance (tSVR) as the ratio of mean systemic arterial pressure (mSAP) to CO. The end-systolic pressure-volume ratio (SP/ESV) was calculated as mPAP/RVESV for the RV and as (0.9*systolic blood pressure)/LVESV for the LV, as previously described[18, 19]. NT-proBNP was analysed from venous blood samples.

Statistical analysis

Data were analysed using IBM SPSS statistics 22 software. Gaussian distribution of all continuous variables was confirmed using a Kolmogorov-Smirnov test and values are reported as mean±SD or as median (25% and 75% percentile) as appropriate.. For clinical characteristics, comparisons between groups for continuous variables were performed by one-way ANOVA

whereas the Fisher's Exact or χ^2 test was used for categorical variables. A Mixed Linear Model with compound symmetric covariance matrix and the Bonferroni post-hoc test for multiple comparisons was performed to evaluate the LV and RV volume changes during exercise within and between groups. The interaction between group and workload was included to assess differences between groups. Receiver operating characteristic (ROC) curves were constructed and area under the ROC curves calculated[20] to identify the best echocardiographic and exercise CMR methods for distinguishing athletes with VA from healthy subjects (expressed as area and 95% confidence intervals). Resting, peak-exercise and delta (Δ – change from rest to peak) values were assessed. The significance of differences in area under the curve of the correlated rest and peak exercise ROC curves was tested using the methodology described by Delong et al.[21]

Intra and inter observer variability of echocardiographic measures were assessed at rest and during the three exercise stages in 15 subjects. The mean value of the two observations (x) and the absolute value of the difference between observations (e) ± SD were determined. Reproducibility was assessed by the coefficient of variation CV = (e/x) 100%, the intra class correlation coefficient (two-way mixed and absolute agreement quoted). A p-value <0.05 was considered statistically significant.

Results

The demographic, clinical and exercise echocardiographic characteristics of the four study groups are presented in Table 1. Athletes in each group were of similar age but athletes with arrhythmias had competed in sports for longer and had higher BMIs at the time of the study. Healthy EAs had a higher VO_2peak compared to the other groups, consistent with the fact that the EA-VAs had been advised to de-train. Sixty-five percent of the EA-VAs fulfilled the diagnostic Task Force Criteria for ARVC but none had evidence of familial disease or RV abnormalities that were considered moderate or severe. As detailed in Table 2, the EA-VAs who met major arrhythmia criteria for ARVC were more likely to have been treated with an implantable ICD ($p<0.05$) reflecting the likely influence that sustained ventricular arrhythmias of non-RVOT origin have on clinical decision making. The prevalence of other task force criteria abnormalities was similar between EA-VAs with and without ICDs. The putative risk factor of delayed enhancement on CMR (which is not a listed task force criterion) was observed in one ostensibly healthy EA and no more frequently in EA-VAs. Ventricular ectopy during cardiopulmonary exercise testing was less frequently observed in NAs but was similar in EAs and EA-VAs. Non-RVOT and variable morphology ectopics were similarly observed in all groups, whilst frequent ectopy and non-sustained VT were observed in EA-VAs without an ICD but not in those with an ICD (Table 2).

Echocardiography at rest and during exercise

There were few differences between the groups in resting cardiac measures (Table 3). As would be expected, cardiac volumes and dimensions were greater in the athletes, consistent with typical athletic cardiac remodelling. However, there were no significant differences in functional measures of LV, RV or hemodynamic measures (LVEF, RVFAC, RV S' and PASP) with the exception of RV strain rate which was reduced in EA-VAs as compared with healthy

EAs and NAs (P=0.002) and RV ESPAR which was reduced in EA-VAs as compared with NAs (P=0.011). EA-VAs had larger RV outflow tract dimensions than healthy EAs and NAs whilst RV inflow dimensions and atrial areas were similar amongst the athlete groups but larger than NAs.

Echocardiographic measures were not obtainable in all subjects at peak exercise. Doppler myocardial velocities were obtained in all 34 subjects, LVEF and RVFAC in 32 subjects (94%) and RVESPAR in 24 subjects (71%). Despite this, peak exercise measures demonstrated significant impairment in RV reserve in EA-VAs, whilst LV measures were similar in all groups (Table 3). RV areas were greater whilst RVFAC and RV S' were reduced in EA-VAs relative to both EAs and NAs. These differences are more rigorously defined using repeated exercise measures (Figure 1). During exercise, LVEF augmentation was similar between all groups (interaction between within-subject changes during exercise vs. between-subject groups = 0.84, Figure 1A). In contrast, exercise-induced increases of RVFAC, RV S' and RVESPAR were impaired in EA-VAs relative to EAs and NAs (P<0.0001 for interaction exercise*group; Figure 1B, 1C and 1D). Within the group of EA-VAs, those with an ICD had lower RVFAC (36.0±8.1 vs. 52.1±5.3 %; P<0.0001) and RV S' (12.6±2.6 vs. 16.7±2.9 cm/s; P<0.0001) at peak exercise than those without ICD (P<0.0001). An example of exercise echocardiography comparing RV function in an EA and EA-VA is provided in Figure 2 and Video 1.

NTproBNP did not correlate with resting LV strain (r=-0.31; P=0.09), resting LVEF (r= -0.086, P=0.6) or peak exercise LVEF (r= -0.026, P=0.9). In contrast, NTproBNP correlated modestly with resting RVFAC (r=-0.42; P=0.016), RV S' (r=-0.44; P=0.012) and RV strain (r=-0.57, P<0.01) but a much stronger correlation was found between NTproBNP and peak exercise RVFAC and RV S' (r=-0.78 and -0.71 respectively; P<0.0001; Supplementary Figure 1).

Echocardiographic measures of RV function, pulmonary artery pressures and cardiac output demonstrated excellent reproducibility. Intra-class correlation coefficients ranged between 0.93 and 0.997 for intra-observer variability and between 0.82 and 0.98 for inter-observer variability (Supplementary Table).

CMR-derived cardiac volumes and invasive hemodynamics during exercise

There were no differences in resting cardiac volumes between EAs and EA-VAs reflecting the fact that abnormalities in RV structure and function in the EA-VA group were, at most, mild. As expected, RV volumes in both groups were larger than NAs (P=0.01 and P=0.04, respectively). All resting hemodynamic measures were similar between groups (Table 4).

During exercise, CMR measures were acquired in all subjects without ICDs. At peak exercise, RVEDV and RVESV were significantly larger and RVEF was reduced in EA-VAs relative to EAs and NAs – Table 4. When repeated exercise measures were assessed there was a clear difference between the effect of exercise on RV and LV measures in EA-VAs (Figure 3). Whilst LV function was similar between groups (Figure 3A, C and E), RV function was reduced during exercise. Relative to EAs and NAs, the RV acutely dilated and failed to contract adequately, as demonstrated by a relative increase in RVEDV (interaction p=0.013, Figure 3B) and an attenuated decrease in RVESV (interaction P<0.0001, Figure 3D). As a result, RVEF augmentation was impaired in EA-VAs compared to healthy EAs and NAs (interaction P<0.001; Figure 3F). An example of exercise CMR comparing RV function in an EA and EA-VA is provided in Figure 4 and Video 2.

Increases in SV, HR, mPAP and SBP were similar between the different groups (Table 4). The mPAP/CO slope was similar in EAs, NAs and EA-VAs (0.92±0.42 vs. 1.11±0.46 vs. 1.23±1.1 mmHg/l/min; P=0.64; Figure 5). On the other hand, the augmentation of RV SP/ESV was

reduced in EA-VAs compared to EAs and NAs (P=0.002 for interaction), again in contrast to the change in LV SP/ESV from rest to peak exercise that was similar between groups.

As illustrated in Supplementary Figure 2, there was a strong correlation between echocardiography-derived RVESPAR and CMR-derived RV SP/ESV (r=0.84; P<0.0001).

Impaired RV contractile reserve as a means of identifying arrhythmic risk

ROC curves demonstrated that the ability of RV measures to accurately differentiate EA-VAs from healthy subjects (EAs and NAs) was relatively modest at rest using echocardiography [AUC for RV ESPAR=0.78 (0.61-0.95), RVFAC=0.72 (0.54-0.90) and RV S'=0.71 (0.53-0.90), Figure 6A] but was impressive at peak exercise [AUC = 0.96 (0.89-1.00), 0.89 (0.78-1.00) and 0.90 (0.79-1.00) respectively, Figure 6B). As compared to rest, this represented a significant improvement in AUC for RVESPAR (P=0.02) and a trend for improvement in RVFAC (P=0.052) and RV S' (P=0.054). In the cohort undergoing ex-CMR which excluded EA-VAs with an ICD, resting CMR measures did not differentiate athletes with arrhythmias [AUC for RVESV=0.59 (0.33-0.85), RVEF=0.55 (0.28-0.83), and RV SP/ESV=0.47 (0.15-0.67), respectively, Figure 6C] whereas peak exercise measures did [AUC = 0.86 (0.70-1.00), 0.78 (0.55-1.00), and 0.88 (0.74-1.00) respectively, Figure 6D]. This represented a significant improvement in AUC for all CMR measures at exercise relative to rest (P<0.05). An increase in RVESPAR <3.09 mmHg/cm^2 from rest to peak-exercise had a sensitivity =83% and specificity =100%, whilst an increase in RV SP/ESV <0.25 mmHg/ml had a sensitivity =83% and specificity =88% for identifying athletes with RV arrhythmias.

Discussion

Consistent with our hypothesis that pro-arrhythmic remodelling predominantly affects the RV, we demonstrated that athletes with ventricular arrhythmias develop RV dysfunction during exercise whilst healthy subjects do not. Importantly, this was evident despite there being few abnormalities at rest. This is of considerable clinical significance given that routine clinical assessment of athletes with suspected arrhythmias comprises cardiac imaging at rest, often with a focus on the LV. Our alternative strategy of focusing on the RV during exercise proved far more accurate in identifying athletes with potentially serious arrhythmias and offers considerable promise as a non-invasive risk stratification tool.

Understanding the context of arrhythmias in athletes; the association with RV dysfunction

Intense endurance exercise has been associated with disproportionate RV wall stress and RV injury[5, 7], and we have hypothesized that this may serve as a substrate for complex RV arrhythmias[22]. Given that the hemodynamic load on the RV is minimal at rest and increases disproportionately with exercise intensity[5, 23], it stands to reason that exercise offers an opportunity to identify early or subtle RV dysfunction. Consistent with this premise, there were few differences between EA-VAs and EAs using conventional echocardiographic and CMR measures performed at rest. RVOT dimensions were slightly greater whilst RV systolic strain rate and RVESPAR were slightly lower in EA-VAs as compared with EAs but these measures were of relatively poor predictive value on ROC analysis. On the other hand, every measure of RV function was reduced in EA-VAs during exercise and this was consistently demonstrated using both echocardiography and CMR. Exercise imaging also proved more useful than rhythm analysis given that ventricular ectopics were observed in healthy athletes and those with a predisposition to arrhythmias with equal frequency. Paradoxically, frequent ectopics and non-

sustained VT occurred in those athletes who had been considered at lower risk of sustained arrhythmias and had not been treated with an ICD.

Real-time CMR performed during free breathing and strenuous exercise has been rigorously validated[14] and has the advantage of providing simultaneous comparisons between LV and RV function. Thus, confidence can be placed in the divergence of ventricular function observed in EA-VAs during exercise. In the LV, augmentation of systolic function (reductions in LVESV and increases in LVEF) was similar between EA-VAs, EAs and NAs (Figure 3). In contrast, the reduction in RVESV and the increase in RVEF were significantly attenuated in EA-VAs relative to EAs and NAs. Thus, it can be concluded that the RV is disproportionately affected by exercise and our validation of this concept in humans agrees with pre-clinical rodent models in which endurance exercise promotes pro-arrhythmic remodelling of the RV, whilst sparing the LV[12].

Consistent with previous studies, we observed a near-linear relationship between pulmonary artery pressures and cardiac output (the so-called 'P/Q relationship')[5, 23]. This current data represents the largest published description of invasively determined P/Q ratios in young healthy subjects and confirms that mean pulmonary artery pressures frequently exceed 25mmHg at peak exercise (Figure 5). This represents a 2- to 3-fold increase in systolic load during exercise which is a far greater proportional increase than for the LV and could explain why the RV is most susceptible to exercise-induced dysfunction.

Exercise echocardiography or CMR?

Exercise-induced RV dysfunction in EA-VAs was consistently observed across imaging modalities. Furthermore, there was a strong inverse correlation between measures of RV function at peak exercise and NT-proBNP (Supplementary Figure 1) and also a strong correlation between RV contractility as determined by echocardiography and ex-CMR

(Supplementary Figure 2). Thus, the question arises as to which imaging technique is better. Despite expectations of more accurate quantification of RV function with exercise CMR, it did not prove better than echocardiography at identifying athletes with subtle RV dysfunction and arrhythmias (Figure 6). Given the widespread availability and cost-effectiveness of echocardiography, this is an important finding. Whilst a focus on RV measures is not commonly practiced, the measures employed in this study are relatively simple and could easily be included in clinical routine. During exercise, RVFAC and RV S' were obtained in the majority of subjects and could accurately identify athletes with arrhythmias (Figure 6B). The strongest echocardiographic measure was RVESPAR but its clinical utility may be limited by the fact that it was measurable in only 71% of subjects. In contrast, high quality images can be acquired by Ex-CMR in virtually all subjects but the technique remains expensive and confined to few specialized centres. Although the areas under the ex-CMR ROC curves seemed inferior to those of echocardiography, direct comparison is limited by the fact that athletes with an ICD had to be excluded from CMR assessment. Thus, the ex-CMR study group was smaller and those athletes with the most profound exercise-induced RV dysfunction on echocardiography were excluded. Device exclusions would not be an issue for new presentations in which risk assessment is required and ex-CMR may be an extremely useful adjunct to standard resting CMR performed to exclude structural pathology in athletes with arrhythmias.

Clinical utility of RV stress testing to identify athletes with arrhythmias

It can be extremely difficult to determine the significance of palpitations, isolated ventricular extra-systoles or non-sustained VT in athletes, particularly when traditional cardiac imaging suggests that cardiac morphology and function are normal. From a population of 1644 screened athletes, Dello Russo et al. identified 17 athletes (1%) with frequent ventricular ectopy or non-sustained VT but normal cardiac structure and function by conventional measures[24]. As a means of risk stratification electro-anatomical mapping and a guided ventricular biopsy was performed

revealing myocardial inflammation, fibrosis and/or fatty infiltrates in 13 of 17 athletes. RV angiography[25] and inducibility during an electrophysiology study[2] may also have some prognostic utility. However, ventricular arrhythmias may be identified in 1-3% of endurance athletes[1, 24] and the risks associated with these invasive techniques are not insignificant. There is clear need for a non-invasive means of differentiating healthy athletes from those with potentially serious ventricular arrhythmias. In this context, both exercise-CMR and echocardiographic RV stress testing show promise. ROC curve analyses demonstrated that resting measures of RV function were poor at distinguishing athletes with complex arrhythmias from healthy subjects but that exercise measures were reasonably accurate (Figure 6).

Current clinical recommendations suggest that the absence of structural heart disease is a critical factor in determining the athlete's management and prognosis[26] but the manner in which structural heart disease should be excluded has not been established. Echocardiography and CMR are frequently used in these settings but emphasis tends to be placed on LV measures and imaging is performed at rest. Our current data suggests that this is a flawed practice with poor sensitivity for identifying athletes at risk of serious arrhythmias. We contend that exercise imaging with a focus on RV measures is a critical component of risk stratification in athletes in whom arrhythmias are suspected. Furthermore, there is considerable overlap between the subtle RV changes described here in athletes and those which occur in other cardiac pathologies such as ARVC. As far as we are aware, there are no studies investigating the utility of exercise imaging for ARVC but our data provide strong rationale for such investigations.

Limitations

Our cohort was of modest size and comprised new cases of athletes with arrhythmias as well as cases previously assessed and managed at our institution. As a result, many of the athletes had

received treatment including detraining, anti-arrhythmics and ICDs. This introduces significant confounders in comparisons with the control subjects. However, anti-arrhythmic, beta-blocker and calcium channel blocking medications were withheld for at least 24 hours prior to exercise testing; a period sufficient to exclude any persisting pharmacodynamic effect. Two athletes were treated were with low-dose Amiodarone which may have caused some negative chronotropic effect but would not have been expected to affect measures of biventricular function. As discussed previously, the exclusion of subjects with ICDs may have resulted in underestimation of the extent of RV dysfunction in the EA-VA cohort. Furthermore, there was significant heterogeneity amongst the cohort in terms of the burden and complexity of the arrhythmias, degree of RV remodelling and the amount of prior athletic training. Nonetheless, this represents the largest comparison of athletes with and without ventricular arrhythmias to date, and the only study to investigate exercise measures in this setting.

Conclusions

In endurance athletes, ventricular arrhythmias are associated with RV dysfunction which is most appreciable under the hemodynamic stress of exercise. In athletes with ostensibly normal cardiac function at rest, echocardiographic and CMR measures of RV function performed during exercise show promise in being able to differentiate healthy athletes from those with a propensity to serious ventricular arrhythmias.

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Table 1. Clinical characteristics

	Endurance athletes (n=10)	**Non-athletes (n=7)**	**Endurance athletes with ventricular arrhythmias (n=17)**		**ANOVA p-value**
			No ICD (n=9)	**ICD (n=8)**	
Clinical					
Age (years)	35±6	34±16	39±8	40±9	0.57
BMI (kg/ m^2)	22.9±1.5	23.2±1.7	26.1±3.0 *	26.0±1.9 *	**0.004**
Years of endurance sports	9 (6-17)	0 (0-0)	21 (12-34) §	17 (8-20) §	**0.002**
Hours per week	11 (6-15) §	0.6 (0-2)	11 (7-14) §	15 (14-21) §	**<0.0001**
ARVC Task Force Criteria					
Definite (2 major, 1 major and 2 minor, or 4 minor)			3	8	**0.009**
Borderline (1 major and 1 minor or 3 minor)			0	0	1.0
Possible (1 or 2 minor)			6	0	**0.002**
RVOT ectopics only‡			0	0	1.0
Medications					
beta blockers	-	-	6	5	
calcium antagonists	-	-	2	0	
flecainide	-	-	0	2	
amiodarone	-	-	1	2	
sotalol	-	-	0	2	
cibenzoline	-	-	0	1	
Biochemistry					
NT-proBNP (pg/ml)	32 (12-43)	24 (5-37)	83 (21-294)	132 (68-218)*§	**0.002**
Cardiopulmonary Testing					
VO2peak (ml/min/kg)	54.0±9.7	40.3±3.7 *	38.8±9.1 *	37.3±6.3 *	**<0.0001**
Peak power (Watts)	365±68	261±48 *	328±57	291±42	**0.004**
Peak HR (bpm)	181±7	178±16	174±25	156±14 *	**0.017**
VE/VCO_2 (L/min)	0.026±0.003	0.024±0.004	0.027±0.003	0.027±0.004	0.2

Data presented as mean±SD or median (25% and 75% percentile); P-values from ANOVA using Bonferroni post-hoc test for multiple comparisons.
* P<0.05 for difference vs. EAs; § P<0.05 vs. controls; † P<0.05 vs. EA-VA without ICD
‡ In the absence of any other arrhythmias or structural abnormalities

Table 2. ARVC Task Force Criteria and ectopy observed during exercise testing

		EAs (n=10)	**NAs** (n=7)	**EA-VAs** (n=17)		
				No ICD (n=9)	**ICD** (n=8)	
ARVC task force criteria details						P-value*
Global or regional dysfunction and structural RV alterations	Major	0	0	1	4	0.13
	Minor	0	0	1	0	1.0
Repolarization abnormality	Major	0	0	3	4	0.64
	Minor	2	0	2	3	0.49
Depolarization abnormality	Major	0	0	0	0	1.0
	Minor	NA§	NA§	2	5	0.15
Arrhythmias	Major	0	0	3	7	**0.049**
	Minor	0	0	6	1	**0.049**
Family History	Major	0	0	0	0	1.0
	Minor	0	0	0	0	1.0
Delayed enhancement on CMR	NA†	1	0	1	2	1.0
Ectopy observed during exercise testing						P-value‡
Any Ectopics		5	1	8	6	**0.016**
Non-RVOT morphology		3	1	3	4	0.41
Multiple morphologies		0	0	1	0	0.41
Frequent ectopy (>50 ectopics)		0	0	4	0	**0.006**
Non-sustained VT		0	0	3	0	**0.027**

EAs, endurance athletes; NAs, non-athletes; EA-Vas, endurance athletes with ventricular arrhythmias

*P-value calculated for comparison between EA-VAs with and without ICDs
‡ P-value calculated for comparison between all groups
§NA – Not available: signal averaged ECGs were not performed in control subjects
†Delayed enhancement on CMR is not a recognized task force criterion for ARVC

Table 3. Echocardiographic measures at rest and during exercise

	Endurance athletes (n=10)	**Non-athletes (n=7)**	**Endurance athletes with ventricular arrhythmias (n=17)**	**ANOVA p-value**
Rest				
HR (bpm)	52±8	62±12	55±9	0.220
LV IVSd (mm)	9.7±3.4	9.7±0.7	10.6±1.1	0.184
LV EDV (ml)	142±17	110±9 *	131±24 §	**0.012**
LV ESV (ml)	55±10	47±5	55±17	0.333
LVEF (%)	61.0±4.5	57.4±5.9	58.6±7.0	0.460
LV strain (%)	19.7±2.6	17.7±2.3	18.1±2.8	0.200
LV systolic strain rate (-/s)	1.14±0.20	1.13±0.07	1.0±0.12	0.050
LV s' (cm/s)	8.2±1.4	8.2±1.3	7.1±1.9	0.185
RV diastolic area (cm^2)	27.1±3.4	22.1±2.1 *	30.5±6.1 §	**0.002**
RV systolic area (cm^2)	14.7±1.6	11.6±1.5	18.1±5.1 *§	**0.002**
RVFAC, (%)	45.2±6.2	47.5±6.1	41.1±6.9	0.080
RV strain (%)	26.0±2.5	27.8±2.0	23.8±4.6	0.050
RV systolic strain rate (-/s)	1.51±0.22	1.61±0.19	1.28±0.22 *§	**0.002**
RV s' (cm/s)	11.5±2.4	11.5±1.6	10.0±2.1	0.150
TAPSE (mm)	30±5	25±4	26±4	0.070
PASP (mmHg)	25±5	21±3	23±4	0.340
RV ESPAR ($mmHg/cm^2$)	1.7±0.4	1.9±0.4	1.4±0.4 §	**0.011**
RVOTd (mm)	33±4	32±6	39±8 *§	**0.003**
RVITd (mm)	46±6	41±6	51±4 §	**0.001**
Left atrial area (cm^2)	21.1±3.6	15.8±2.5 *	20.3±2.7 §	**0.002**
Right atrial area (cm^2)	21.1±4.9	16.7±4.0	22.5±3.3 §	**0.010**
Peak Exercise				
HR (bpm)	138±10	129±8	123±20	0.059
LV EDV (ml)	127±22	102±13	122±22	0.050
LV ESV (ml)	31±16	30±3	27±22	0.836
LVEF (%)	74.2±5.9	70.9±2.3	69.3±8.5	0.290
LV s' (cm/s)	13.5±1.3	13.6±2.4	10.9±3.2	0.185
LV e' (cm/s)	16.9±2.8	15.6±2.8	13.6±3.7	0.363
RV diastolic area (cm^2)	25.8±2.2	20.9±1.9	30.5±6.2 *§	**0.001**
RV systolic area (cm^2)	11.1±1.6	8.9±1.0	17.4±6.4 *§	**0.001**
RVFAC, (%)	57.1±5.2	57.0±5.2	44.1±10.6 *§	**0.001**
RV s' (cm/s)	18.9±1.2	20.6±2.9	14.6±3.4 *§	**<0.0001**
PASP (mmHg)	61±7	49±10 *	48±9 *	**0.010**
RV ESPAR ($mmHg/cm^2$)	5.7±1.1	5.6±1.5	3.0±1.2 *§	**<0.0001**

*P<0.05 for difference vs. EAs; §P<0.05 vs. NAs. P-values from ANOVA using Bonferroni post-hoc test for multiple comparisons.

Table 4. CMR measures at rest and during exercise

	Endurance athletes (n=10)	**Non-athletes (n=7)**	**Endurance athletes with ventricular arrhythmias (n=9)**	**ANOVA p-value**
Rest				
HR (bpm)	59±8	67±7	61±12	0.23
CO (L/min)	8.1±1.0	7.4±1.5	7.7±1.7	0.63
LVEDV (ml)	225±18	196±23 *	229±24 §	**0.01**
LVESV (ml)	86±10	85±17	100±32	0.3
LVSV (ml)	139±14	111±17 *	129±22	**0.012**
LVEF (%)	61.8±3.3	56.6±5.9	56.8±10.2	0.22
RVEDV (ml)	237±28	200±22	233±34	**0.04**
RVESV (ml)	99±13	90±14	108±31	0.3
RVSV (ml)	138±19	110±13 *	125±21	**0.02**
RVEF (%)	58.0±2.9	55.1±3.7	54.1±8.1	0.29
mSAP (mmHg)	96±7	89±7	93±6	0.11
mPAP (mmHg)	14±4	11±2	15±4	0.09
tSVR	964±152	984±181	1009±248	0.88
tPVR	136±38	118±27	168±78	0.18
Peak exercise				
HR (bpm)	161±12	151±9	149±25	0.30
CO (L/min)	24.0±2.6	19.5±3.6	21.5±5.1	0.077
LVEDV (ml)	218±14	186±25 *	224±19 §	**0.001**
LVESV (ml)	65±16	57±10	79±28	0.096
LVSV (ml)	153±17	129±18	145±21	0.055
LVEF (%)	70.1±6.6	69.5±3.9	65.2±10.0	0.34
RVEDV (ml)	214±28	179±22 *	237±27 §	**0.001**
RVESV (ml)	67±19	52±10	95±30 *§	**0.002**
RVSV (ml)	147±22	127±17	142±24	0.19
RVEF (%)	68.7±6.9	70.9±4.1	60.3±10.4 §	**0.025**
mSAP (mmHg)	129±10	116±10	126±12	0.074
mPAP (mmHg)	28±7	23±6	30±10	0.303
tSVR	435±67	489±89	492±136	0.40
tPVR	94±31	98±29	121±74	0.48

*P<0.05 for difference vs. EAs; §P<0.05 vs. NAs. P-values from ANOVA using Bonferroni post-hoc test for multiple comparisons.

Supplementary Table 1: Observer variability for echocardiographic exercise measures

	Intra-observer			Inter-observer		
	CV, %	Intra class correlation coefficient (95% Confidence Interval)	Mean Difference ±SD	CV, %	Intra class correlation coefficient (95% Confidence Interval)	Mean Difference ±SD
LVOT VTI (cm)	3.0	0.98 (0.83 – 0.99)	0.74 ±0.7	2.1	0.98 (0.95 – 0.99)	0.52 ±0.96
RV EDA (cm^2)	8.6	0.93 (0.14 – 0.98)	2.6 ±1.8	6.0	0.90 (0.75 – 0.95)	1.8 ±3.1
RV ESA (cm^2)	9.5	0.95 (0.69 – 0.98)	1.6 ±1.7	12.3	0.92 (0.60 – 0.97)	2.1 ±2.3
RVFAC (%)	1.1	0.93 (0.87 – 0.96)	0.50 ±4.8	8.0	0.82 (0.66 – 0.90)	3.5 ±7.4
PASP (mmHg)	0.7	0.997 (0.99 – 1.00)	0.24 ±1.36	1.5	0.98 (0.97 – 0.99)	0.52 ±3.5
RV ESPAR ($mmHg/cm^2$)	7.2	0.99 (0.94 – 0.99)	0.17 ±0.22	6.5	0.96 (0.93 – 0.98)	0.15 ±0.50
RV S' (cm/s)	1.1	0.97 (0.99 – 1.00)	0.15 ±0.50	2.6	0.97 (0.95 – 0.98)	0.35 ±1.3

CV, coefficient of variation; SD, standard deviation; LVOT VTI, LV outflow tract velocity time integral; RVEDA, RV end-diastolic area; RVESA, RV end-systolic area; RVFAC, RV fractional area change; PASP, systolic pulmonary artery pressure; RV ESPAR, RV End-systolic pressure area relationship; RV S', RV systolic annular velocity.

Figure legend:

Figure 1. Echocardiographic measures demonstrating reduced RV reserve in athletes with arrhythmias.

Changes in (A) LV ejection fraction (LVEF), (B) RV fractional area change (RVFAC), (C) RV peak systolic tricuspid annular velocity (RV S') and (D) RV end-systolic pressure-area relationship (RV ESPAR) from rest to peak exercise. P values are shown for the interaction between group and exercise-intensity. At each exercise intensity, * P<0.05 for the difference between EA-VAs and EAs and § P<0.05 for the difference between EA-VAs and NAs. Error bars depict the standard error of the mean.

Figure 2. Reduced exercise RV function in an athlete with arrhythmias as compared with normal exercise RV function in a healthy endurance athlete.

End-systolic images of the RV are depicted at rest and at peak-exercise in a healthy endurance athlete (EA) and an athlete with ventricular arrhythmias (EA-VA). There is a clear reduction in RV end-systolic area from rest to peak exercise in EA resulting in an appropriate increase in RV fractional area change (RVFAC) whereas the RV area does not decrease in EA-VA and the RVFAC does not increase. The difference in RV augmentation is even better appreciated in video format (see Video 1).

Figure 3. Magnetic resonance derived biventricular volume changes during exercise

Changes in EDV, end-diastolic volume; ESV, end-systolic volume; and EF, ejection fraction during incremental exercise are shown for EA-VAs (red), EAs (green) and NAs (blue). P-values are shown for the interaction between group and exercise-intensity. At each exercise intensity, *P<0.05 for the difference between EA-VAs and EAs and § P<0.05 for the difference between EA-VAs and NAs. Error bars depict the standard error of the mean.

Figure 4. Reduced exercise RV function in an athlete with arrhythmias as compared with normal exercise RV function in a healthy endurance athlete.

End-systolic images are depicted at rest and at peak-exercise in a healthy endurance athlete (EA) and an athlete with ventricular arrhythmias (EA-VA). In EA, there is augmentation of both LV and RV function with exercise and the RV ejection fraction increases from 56% to 74%. Resting RV function is similar in EA and EA-VA, but RV function fails to augment in EA-VA. The difference in RV augmentation is even better appreciated in video format (see Video 2).

Figure 5. Relationship between mean pulmonary artery pressure and cardiac output. The relationship between mPAP and CO is similar for EAs, NAs and EA-VAs as indicated by the fact that there is no significant interaction between groups and the mPAP/ CO relationship. Error bars depict the standard error of the mean.

Figure 6. Receiver-operating characteristic (ROC) curves for echocardiographic and CMR measures of RV function at rest and during exercise.

Areas under curve (AUC) represent test accuracy in differentiating athletes with arrhythmias from healthy athletes and non-athletes. AUCs for RV fractional area change (RVFAC), RV peak systolic tricuspid annular velocity (RV S') and RV end-systolic pressure-area relationship (RV ESPAR) improved from rest to exercise (Panels A and B, $P \leq 0.05$). Resting CMR measures (ESV, end-systolic volume; EF, ejection fraction; SP/ESV, end-systolic pressure volume relationship) could not differentiate a smaller cohort of athletes with arrhythmias from healthy subjects (Panel C), but all AUCs improved ($P<0.05$) and demonstrated good accuracy during exercise (Panel D).

Supplementary Figure 1. Correlations between B-type natriuretic peptide and RV function during exercise.

Scatter plots and Pearson's correlation statistics for the association between NTproBNP and (A) peak exercise RV fractional area change (RVFAC) and (B) RV peak-systolic velocity (RV S').

Supplementary Figure 2. Correlations between echocardiographic and magnetic resonance derived surrogates of RV contractility during exercise.

Scatter plots and Pearson's correlation statistics for the association between the echocardiographic RV end-systolic pressure area relationship (RVESPAR) and the cardiac magnetic resonance and invasive RV systolic pressure volume relationship (RV SP/ESV).

Video 1. Reduced exercise RV function in an athlete with arrhythmias as compared with normal exercise RV function in a healthy endurance athlete – an echocardiographic example.

Video 2. Reduced exercise RV function in an athlete with arrhythmias as compared with normal exercise RV function in a healthy endurance athlete – a CMR example.

Figure 1

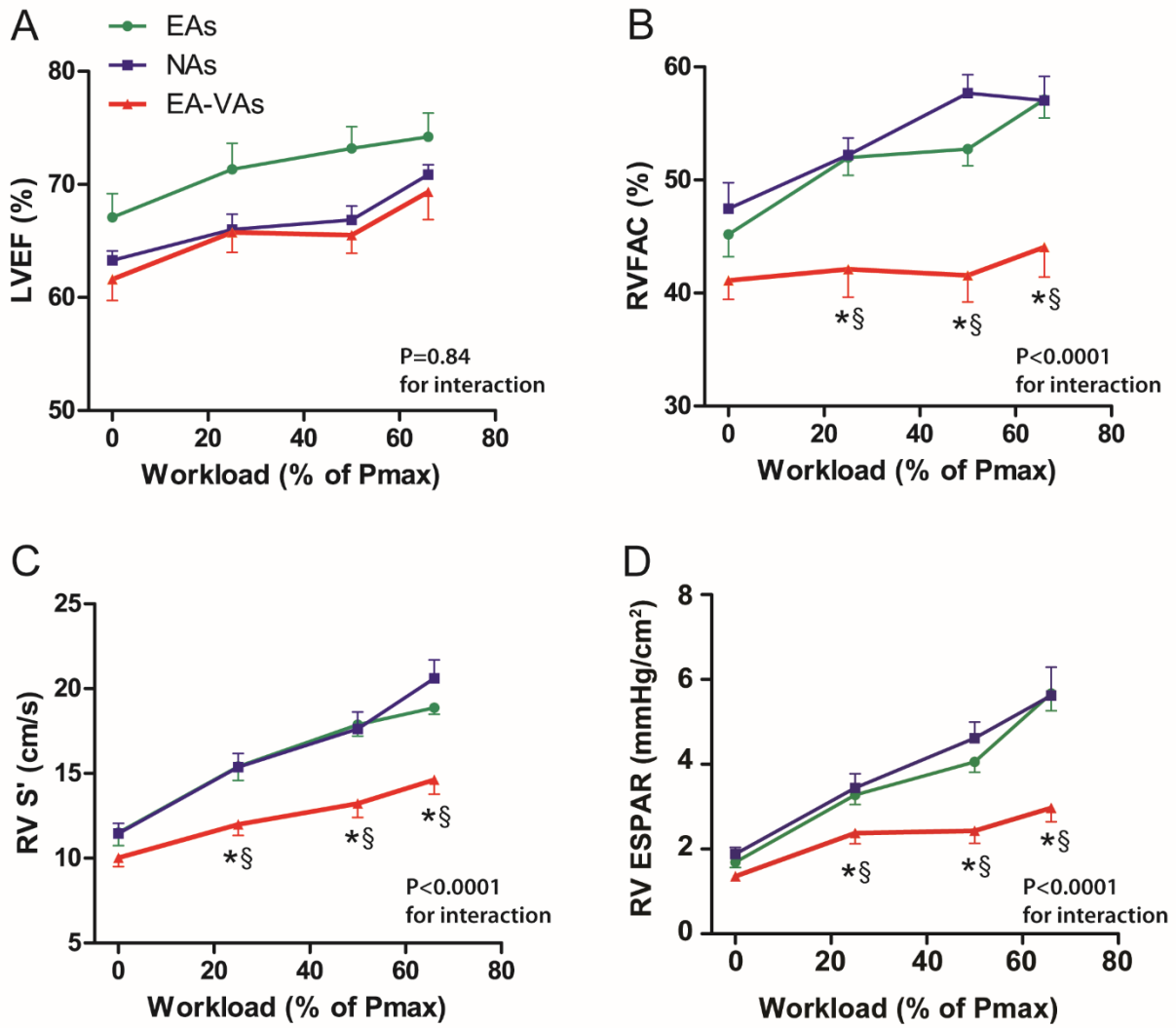

A
EAs
NAs
EA-VAs
LVEF (%)
80
70
60
50
0
20
40
60
80
Workload (% of Pmax)
P=0.84
for interaction
B
RVFAC (%)
60
50
40
30
*§
*§
*§
P<0.0001
for interaction
Workload (% of Pmax)
C
RV S' (cm/s)
25
20
15
10
5
*§
*§
*§
P<0.0001
for interaction
Workload (% of Pmax)
D
RV ESPAR (mmHg/cm²)
8
6
4
2
0
*§
*§
*§
P<0.0001
for interaction
Workload (% of Pmax)

Figure 2

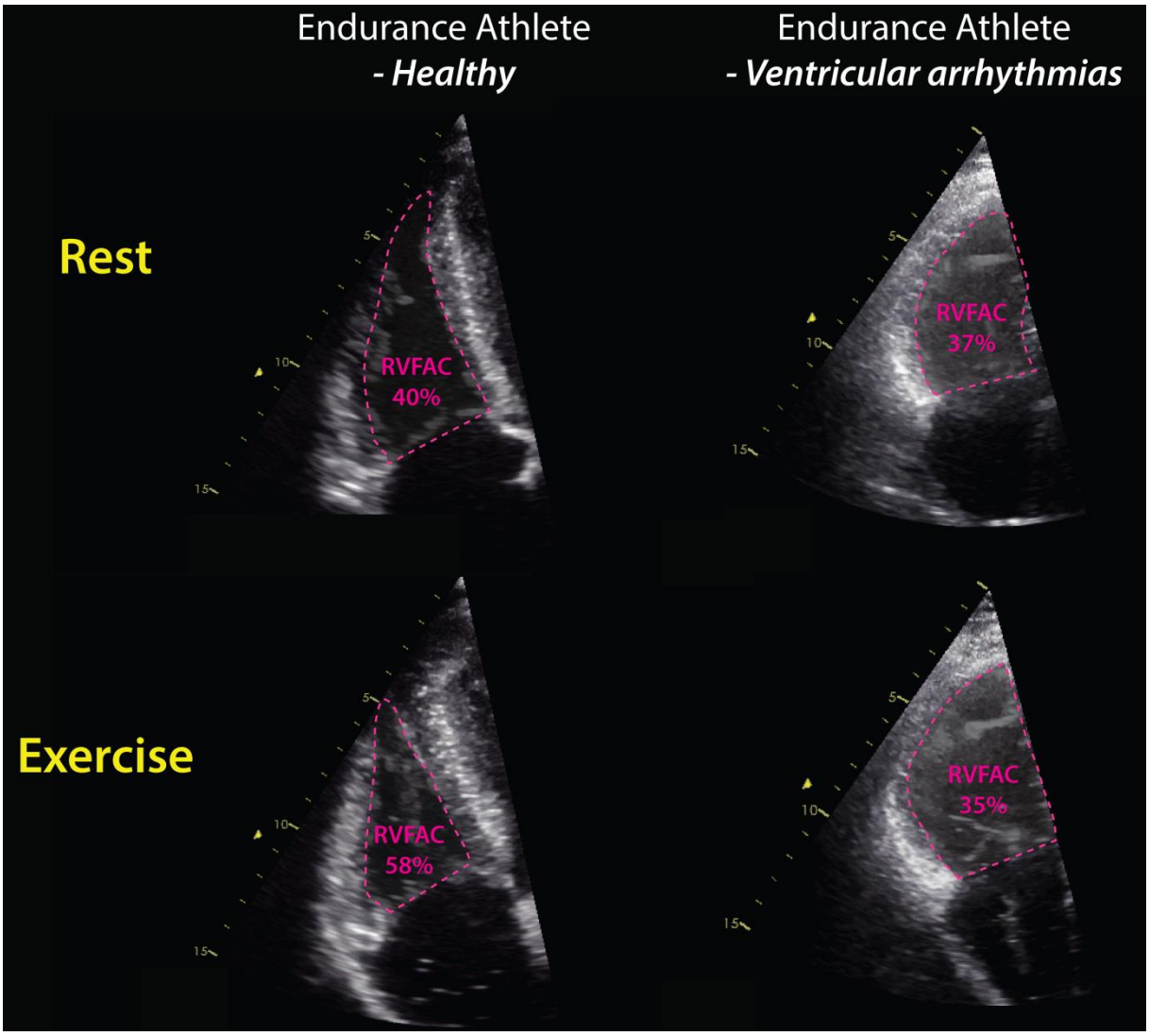

Endurance Athlete
- Healthy
Endurance Athlete
- Ventricular arrhythmias
Rest
Exercise
RVFAC
40%
RVFAC
37%
RVFAC
58%
RVFAC
35%

Figure 3

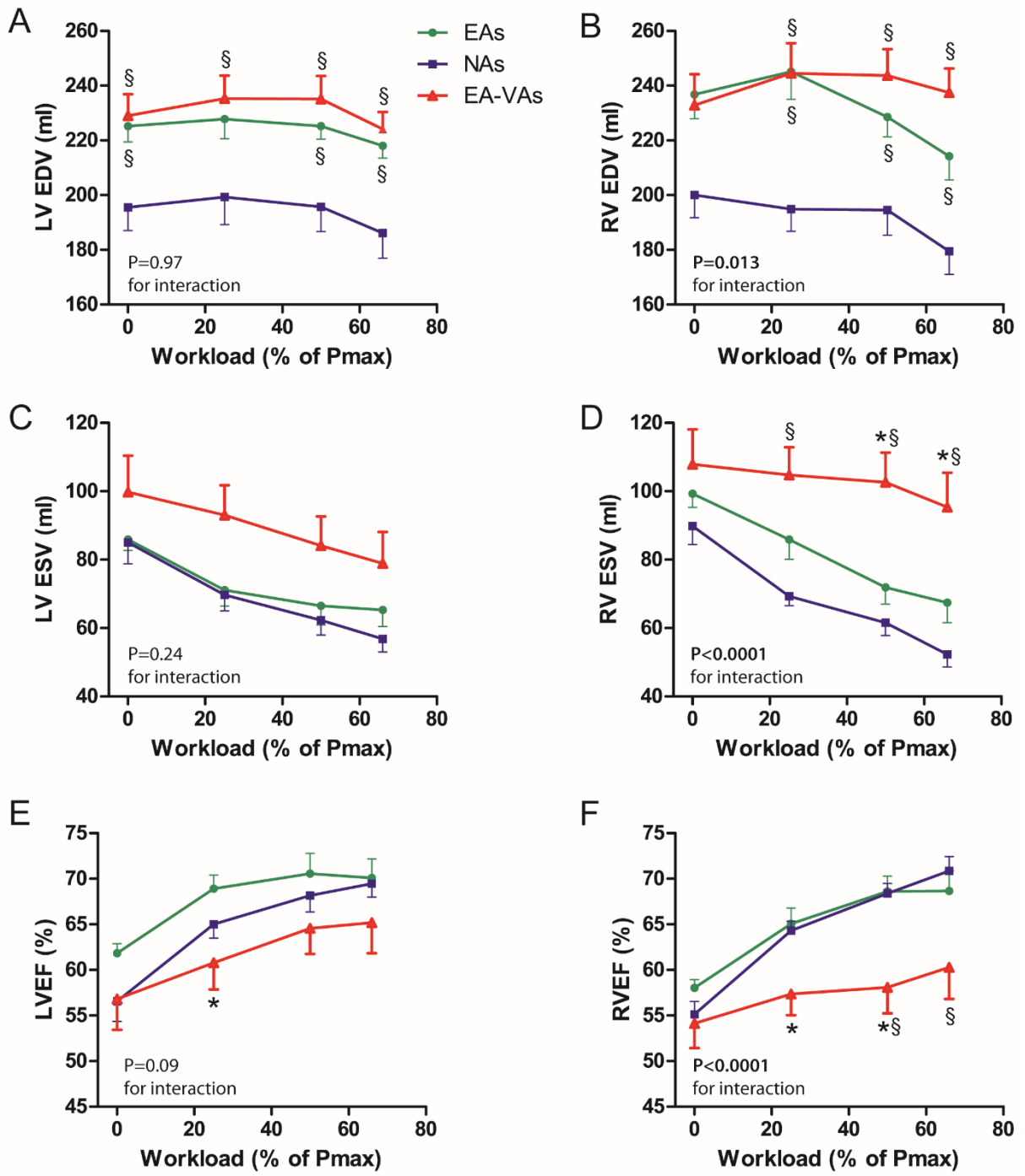

A
LV EDV (ml)
EAs
NAs
EA-VAs
P=0.97
for interaction
Workload (% of Pmax)
B
RV EDV (ml)
P=0.013
for interaction
Workload (% of Pmax)
C
LV ESV (ml)
P=0.24
for interaction
Workload (% of Pmax)
D
RV ESV (ml)
P<0.0001
for interaction
Workload (% of Pmax)
E
LVEF (%)
P=0.09
for interaction
Workload (% of Pmax)
F
RVEF (%)
P<0.0001
for interaction
Workload (% of Pmax)

Figure 4

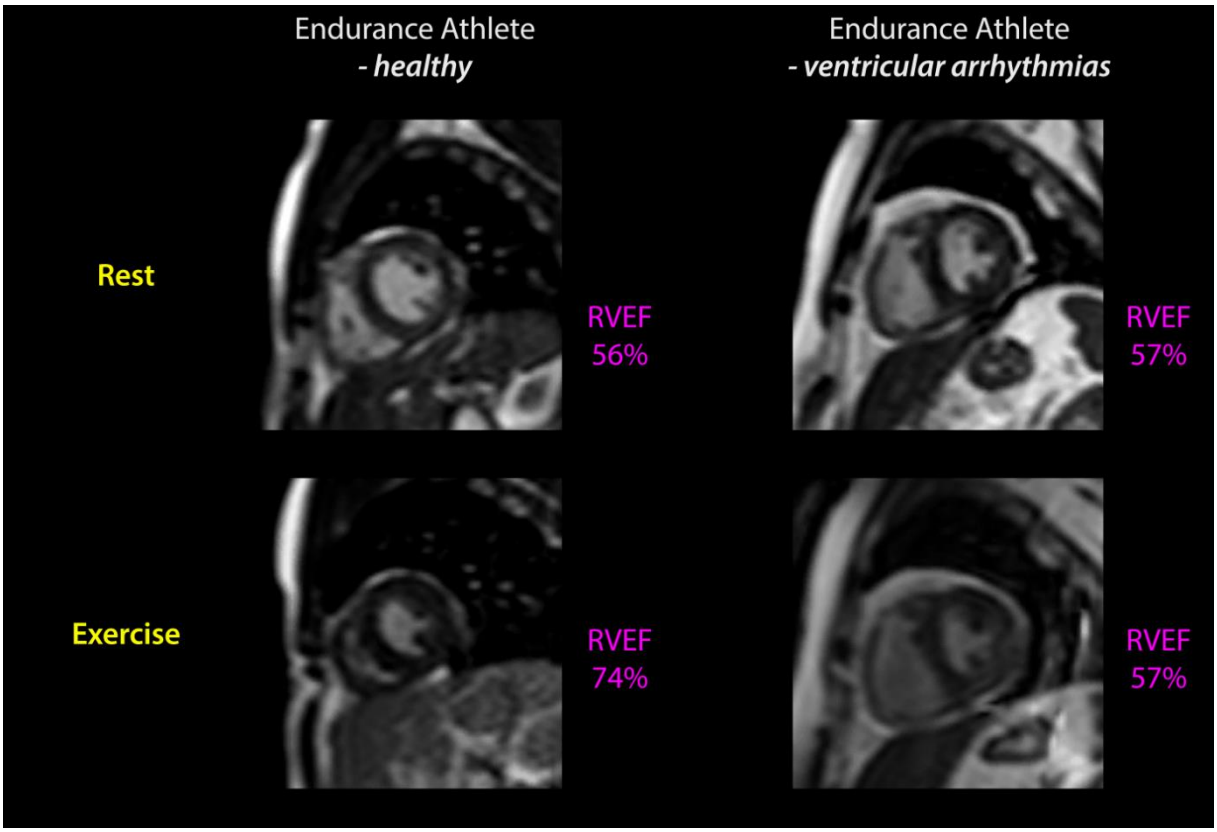

Endurance Athlete
- healthy
Endurance Athlete
- ventricular arrhythmias
Rest
RVEF
56%
RVEF
57%
Exercise
RVEF
74%
RVEF
57%

Figure 5

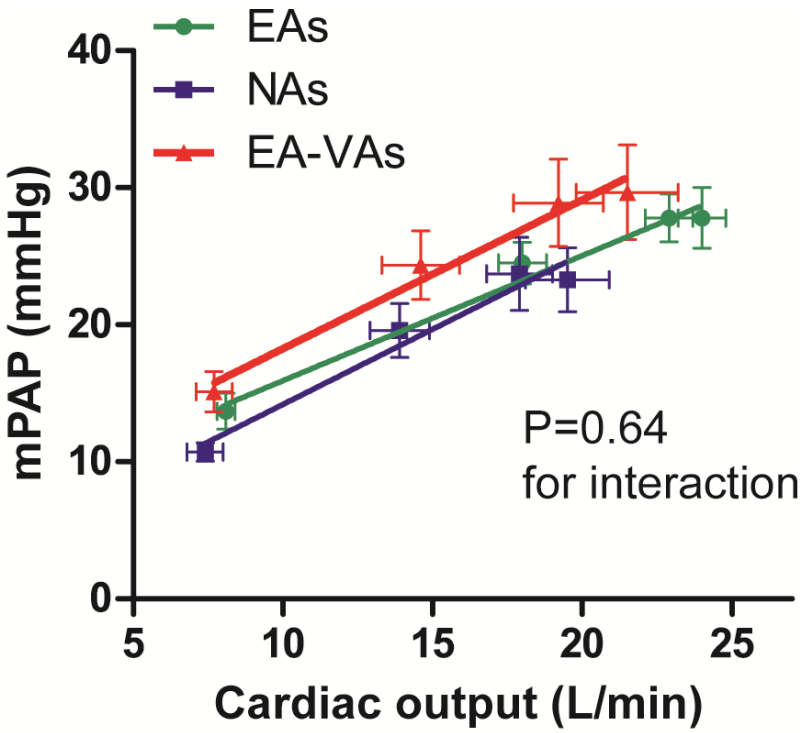
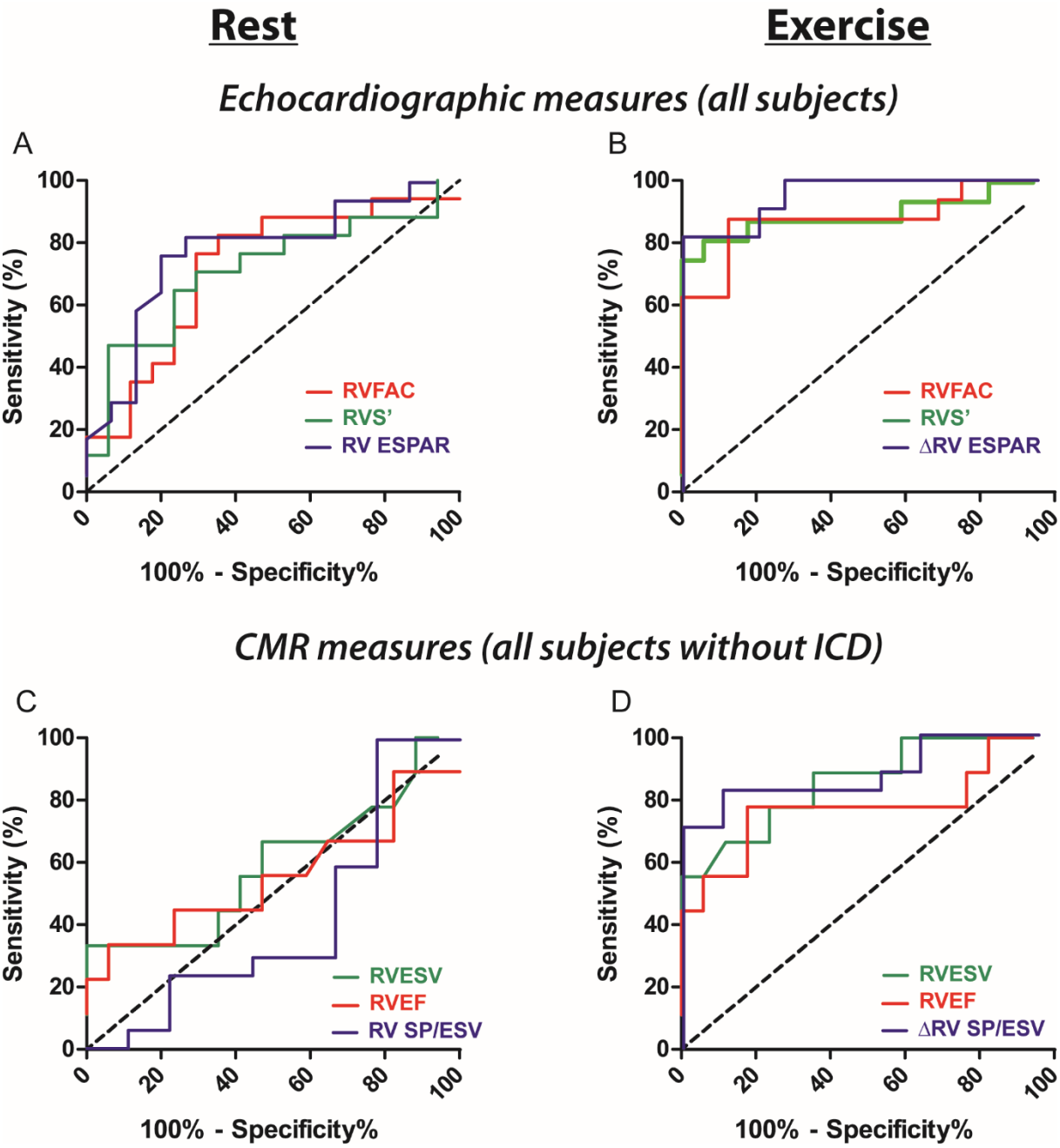
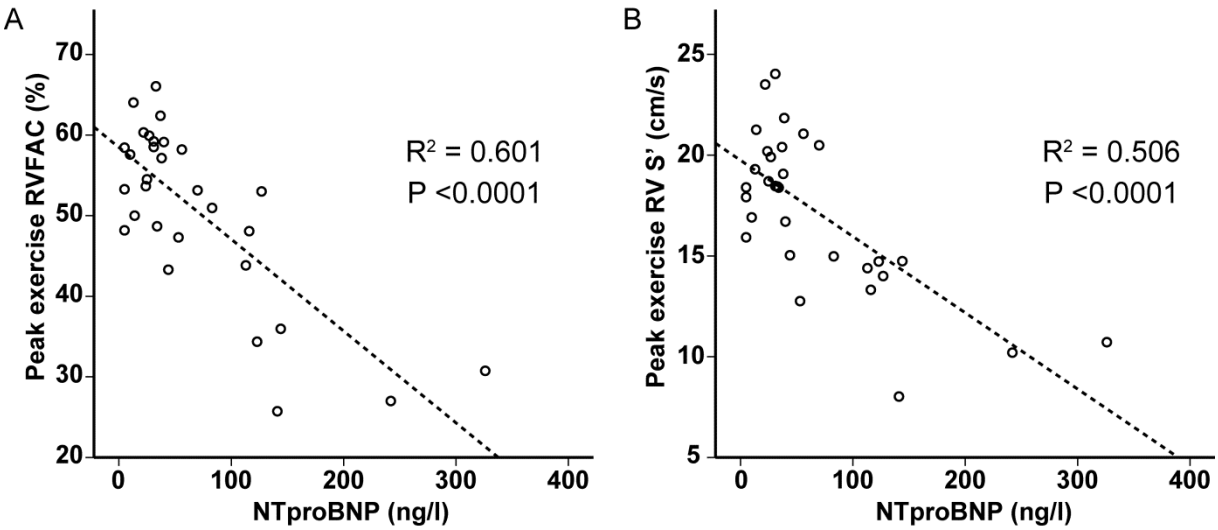

EAs
NAs
EA-VAs
mPAP (mmHg)
40
30
20
10
0
5
10
15
20
25
Cardiac output (L/min)
P=0.64
for interaction

Figure 6


Rest
Exercise
Echocardiographic measures (all subjects)
A
B
Sensitivity (%)
100% - Specificity%
RVFAC
RVS'
RV ESPAR
ΔRV ESPAR
CMR measures (all subjects without ICD)
C
D
RVESV
RVEF
RV SP/ESV
ΔRV SP/ESV

Supplementary Figure 1. Association between B-type natriuretic peptide and RV function during exercise.

Scatter plots and coefficient of determination for the association between NTproBNP and (A) peak exercise RV fractional area change (RVFAC) and (B) RV peak-systolic velocity (RV S').



Supplementary Figure 2. Association between echocardiographic and magnetic resonance derived surrogates of RV contractility during exercise.

Scatter plots and coefficient of determination for the association between the echocardiographic RV end-systolic pressure area relationship (RVESPAR) and the cardiac magnetic resonance and invasive RV systolic pressure volume relationship (RV SP/ESV).